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Novel Formulation and Biopharmaceutical Challenges of Oral Cancer Therapy

Gavin Halbert
Cancer Research UK Formulation Unit
Strathclyde Institute of Pharmacy and Biomedical Sciences
University of Strathclyde

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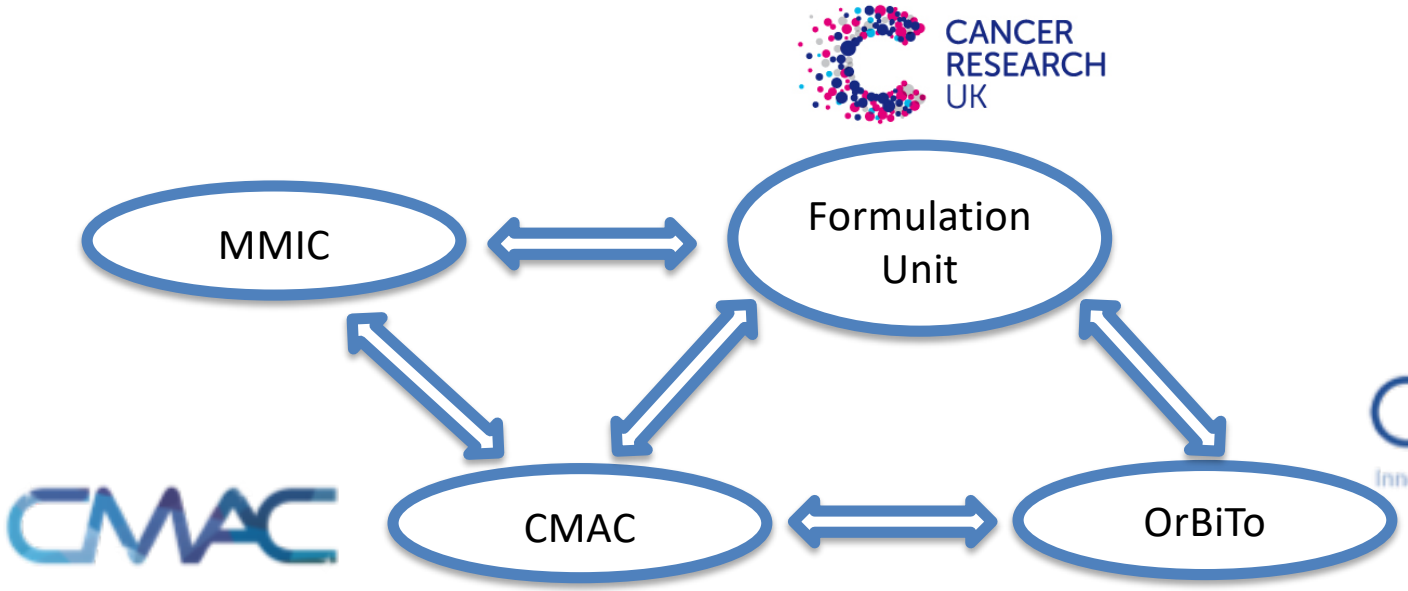
Synopsis

- Introduction
- Oral administration
- Cancer and chemotherapy developments
- Barriers requiring carriers
- Pharmaceutical nanolandscape
- Amorphous, anthracyclines and taxanes
- Nanotechnology issues
- Conclusions

Gavin Halbert

- Pharmacist, Chemist & Qualified Person
- Drugs into patients
- Range of research, formulation and product experience
- Drug delivery sympathies – practical realities



Formulation Unit

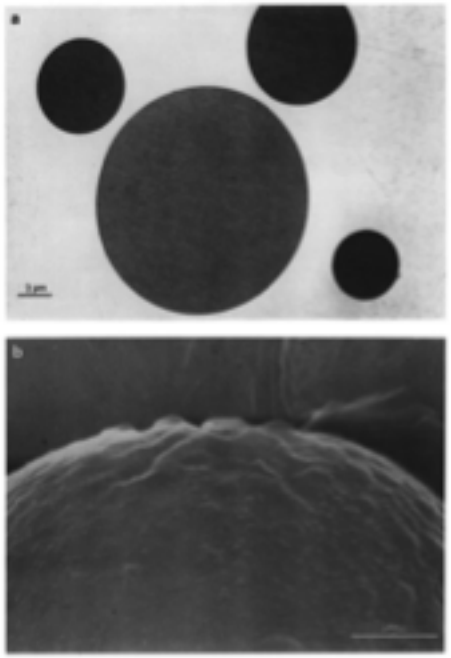
- Established in 1983 – unique within UK
- Develop novel anti-cancer drugs selected by Cancer Research UK
- Antibodies – Alkylating Agents – Antisense
- Drug Delivery Systems
  - Liposomes
  - ADEPT

Introduction

Drug Delivery in Cancer Chemotherapy

- Long history of delivery/targeting drugs to cancer
  1958 – methotrexate conjugated to polyclonal antibody
- Early rationale
  Alleviation of toxicity
- Multiple systems tested
  Liposomes
  Microspheres
  Nanoparticles
  Polymeric conjugates

Microscopy Transferrin/Albumin/Polyaspartic acid microspheres



Chen, Y., et.al., J.Cont.Rel., 1988;8;93-101

Oral Nanoparticulate Systems

- Uptake of nanoparticles after gastro-intestinal administration

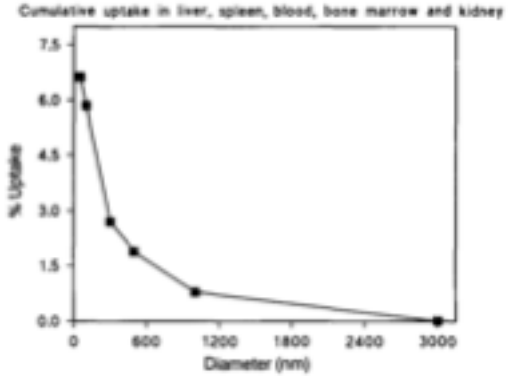
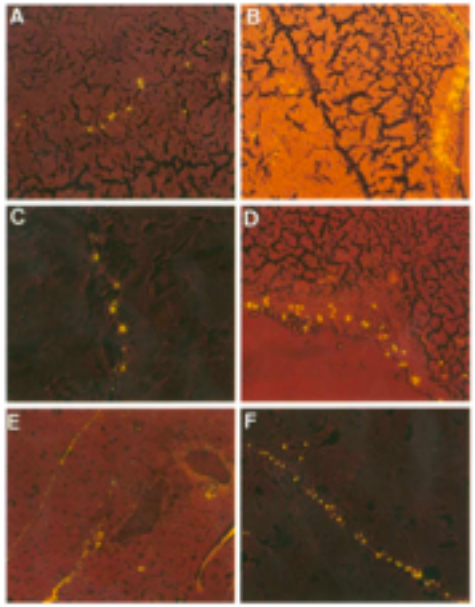


Fig. 7. The cumulative uptake of polystyrene, orally administered to female Sprague Dawley rats for 10 days at a dose of 1·25 mg kg^{-1}, as a function of particle diameter in the liver, spleen, blood, bone marrow and kidney. In the case of particles of 500 nm and 1 μm these data refer only to liver and spleen as no microspheres were detected in blood, bone marrow and kidney. For the 300 nm latex the data refer to liver, spleen and blood.

Jani, P., et.al., J.Pharm.Pharmacol., 1990;42;821-826
Jani, P., et.al., J.Pharm.Pharmacol., 1989;41;809-812



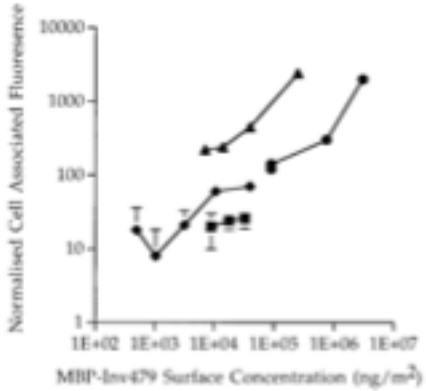


Fig. 7. Effect of MBP-Inv479 surface density and nanoparticle size upon cellular association. Cell incubation performed using standard conditions; ♦ 155 nm diameter PLGA nanoparticles; ■ 200 nm; ▲ 375 nm; ● 600 nm. Mean association n = 3 ± standard deviation. PLGA has a density of 1.39 g/cm^3, therefore the total surface area for a given nanoparticle mass can be calculated based on the measured hydrodynamic diameter. The amount of bound protein can be measured and the degree of protein coverage expressed as a quantity bound per unit surface area (ng/m^2).

Dawson, G.F., Halbert, G.W., Pharm.Res., 2000;17;1420-1425

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Cancer and chemotherapy developments

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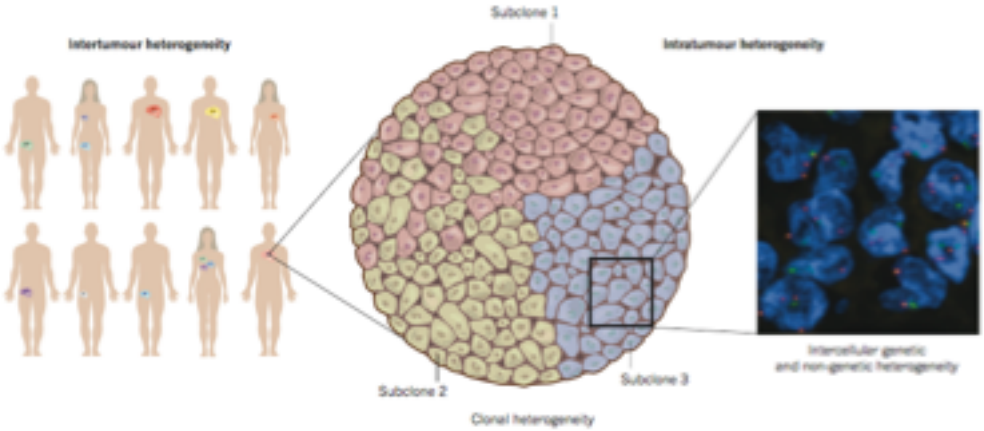
Cancer Research

- Massive increase in biological understanding
- Imatinib – 2001 – targeted treatment
- Tumour heterogeneity
- Agile combination therapy
- Personalised therapy



Burrell, R., et.al., (2013) Nature 501: 338-345

Cancer and chemotherapy developments

Molecular Complexity
BCS Issues

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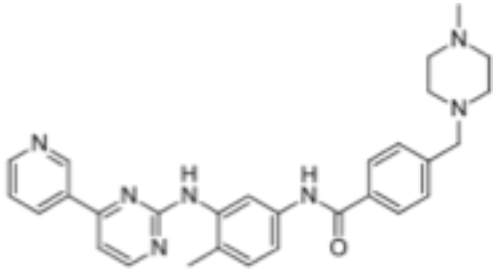
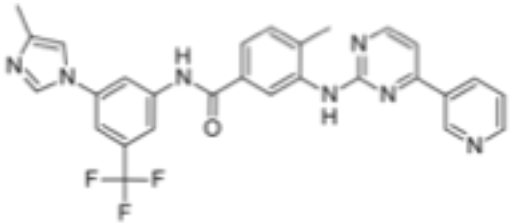
imatinib



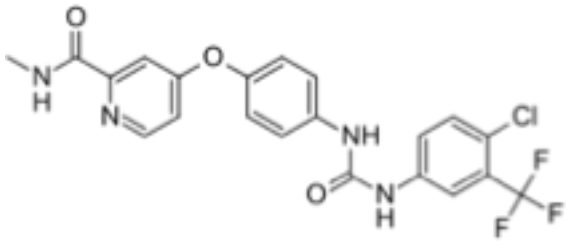
Solubility 200mg/ml
Oral Bioavailability 98%

nilotinib



Solubility sparingly
Oral Bioavailability 31%

sorafenib



Solubility (1:2 DMSO:PBS) 0.3mg/ml
Oral Bioavailability 50%

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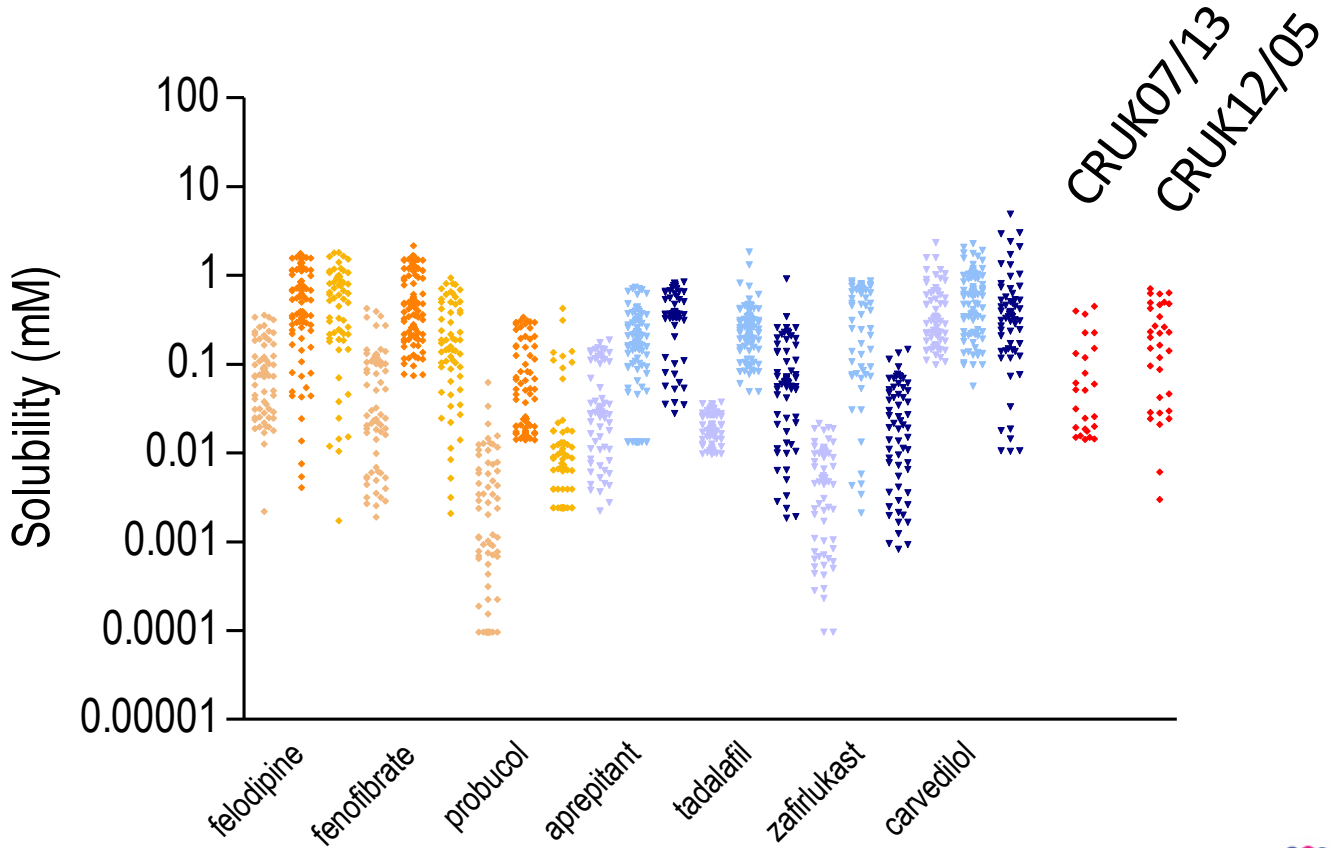
Cancer and chemotherapy developments

Intestinal Solubility Variation

- Impact of simulated gastrointestinal fluid composition



Khadra, I., et.al., (2015) Eur. J. Pharm. Sci., 67: 65-75 (Fasted data only)

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Oral administration

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Cancer Chemotherapy Therapy Routes of Administration

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- Oral therapy – always present
  - Chlorambucil, tamoxifen
  - Traditional formulation presentations
    - Not always optimal
- Parenteral therapy – main route
  - Alkylating agents, doxorubicin
  - Bioavailability
  - Acute therapy
    - Toxicity, pharmacokinetics

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Oral administration

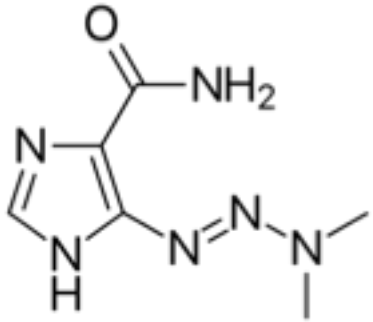
Oral Therapy - Temozolomide

- Dacarbazine

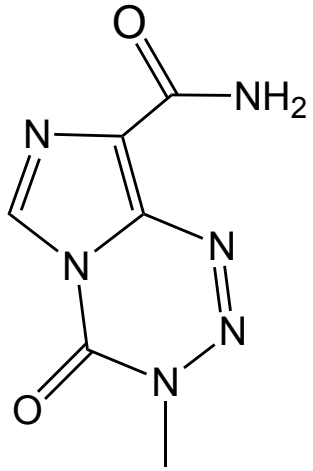
  IV administration

- Temozolomide

  Oral administration



Dacarbazine



Temozolomide

Pro-drug approach

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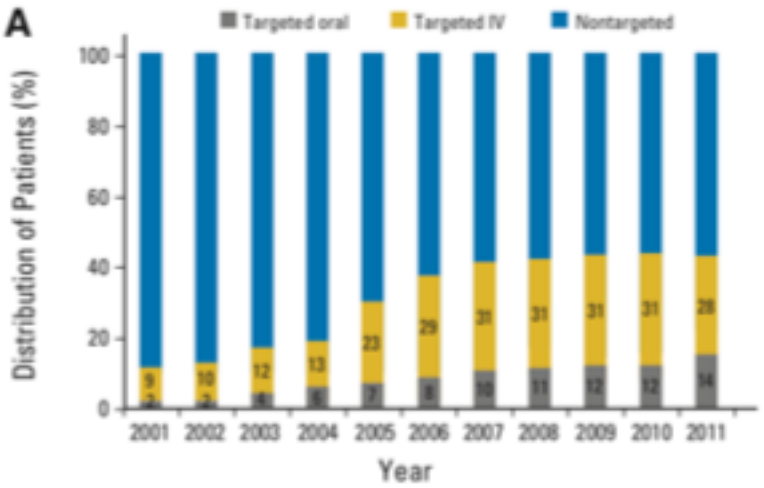
Oral administration

Advantages and switch to oral

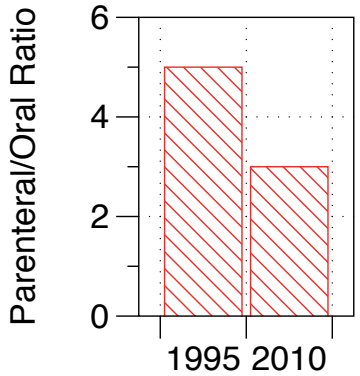
"the most frequently reported attributes contributing to preference included convenience, ability to receive treatment at home, treatment schedule, and side effects."

EeK, D., et.al., Patient Preference and Adherence 2016;10;1609-1621



Shih, Y-C.T., et.al., J.Clin.Oncol., 2015;33;2190-2196

Formulation Unit Survey

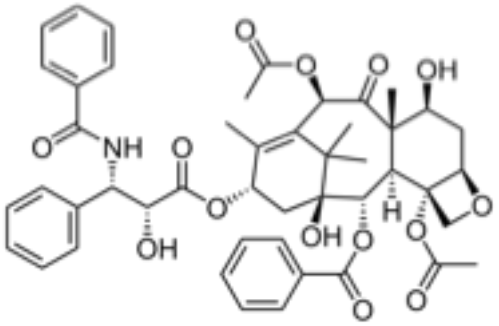


"Biotechs" not included

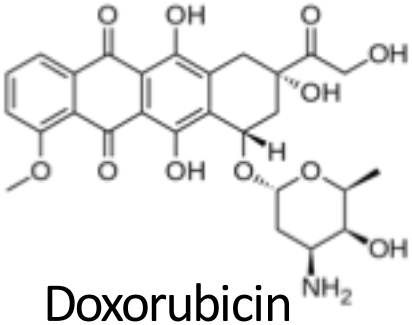
Oral administration

Bioavailability

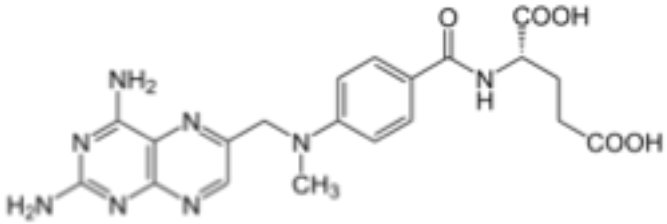
- Poor bioavailability - always an issue
- Chemical stability
- Poor solubility
- Efflux pumps



Paclitaxel



Doxorubicin



Methotrexate

Oral administration

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Barriers requiring carriers

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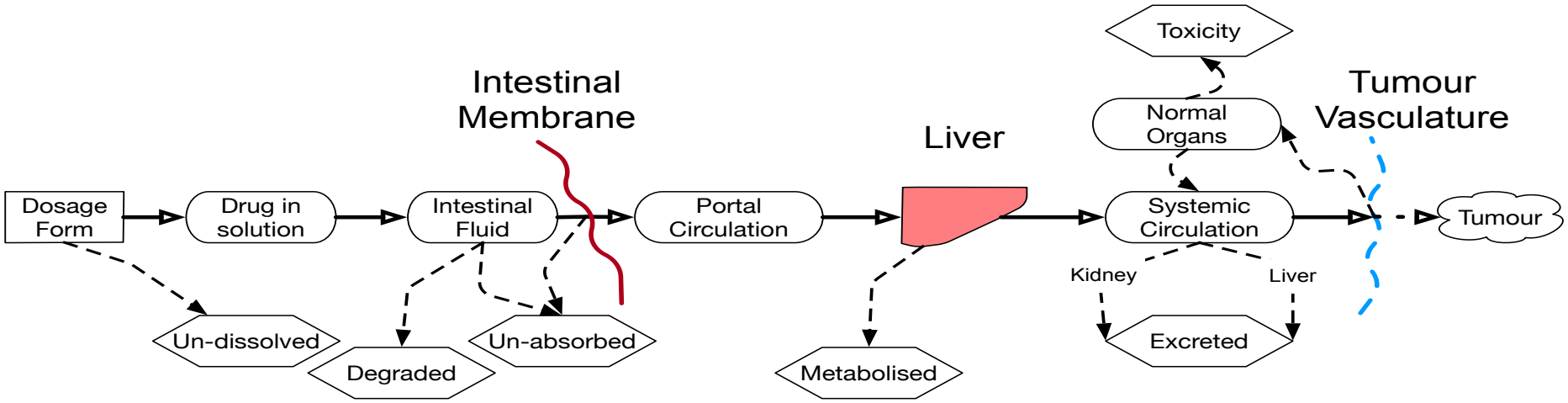
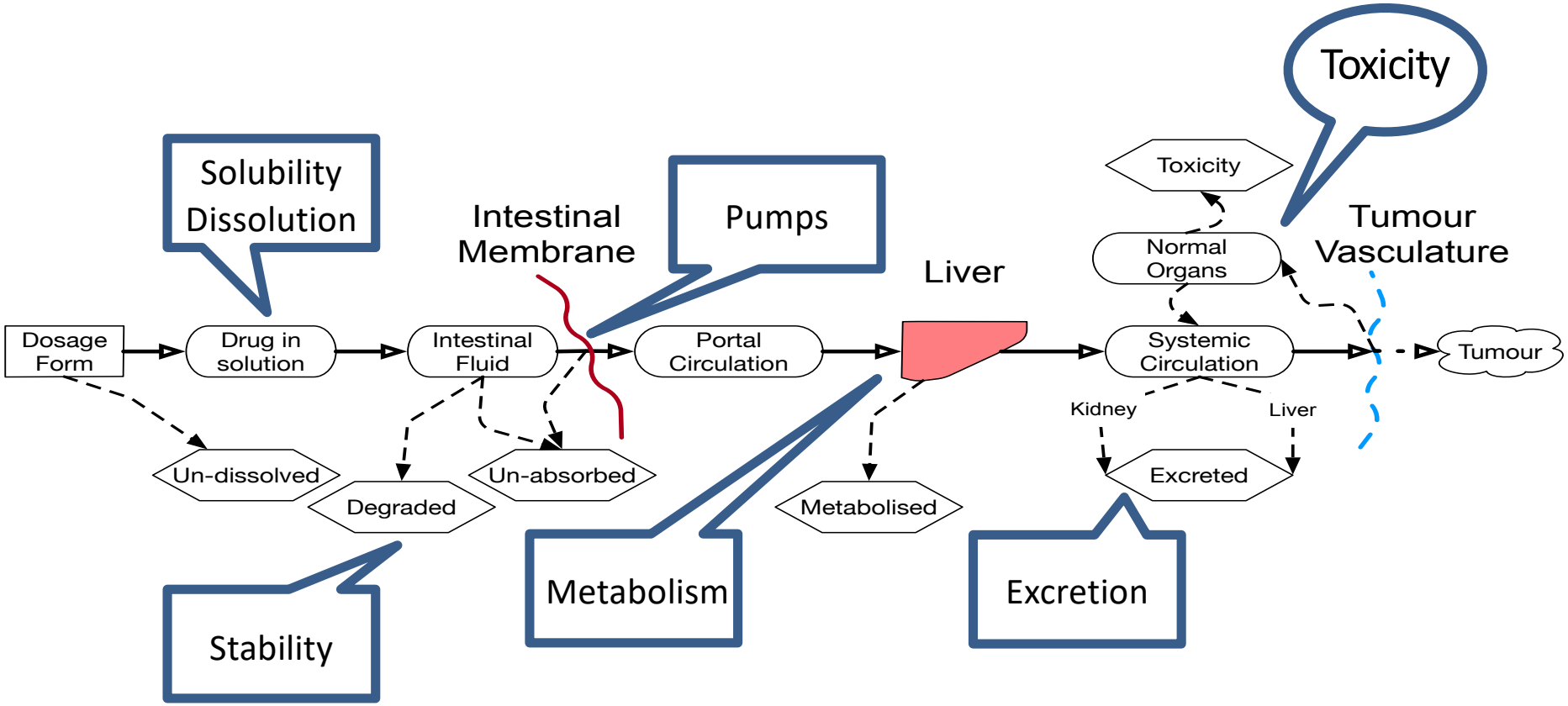
Gastrointestinal transit route



Reviews
Blanco, E., et.al., Nat.Biotechnol., 2015;33;941-951
Malhaire, H., et.al., Adv.Drug.Deliv.Rev., 2016;106;320-336

Barriers requiring carriers

Gastrointestinal transit route



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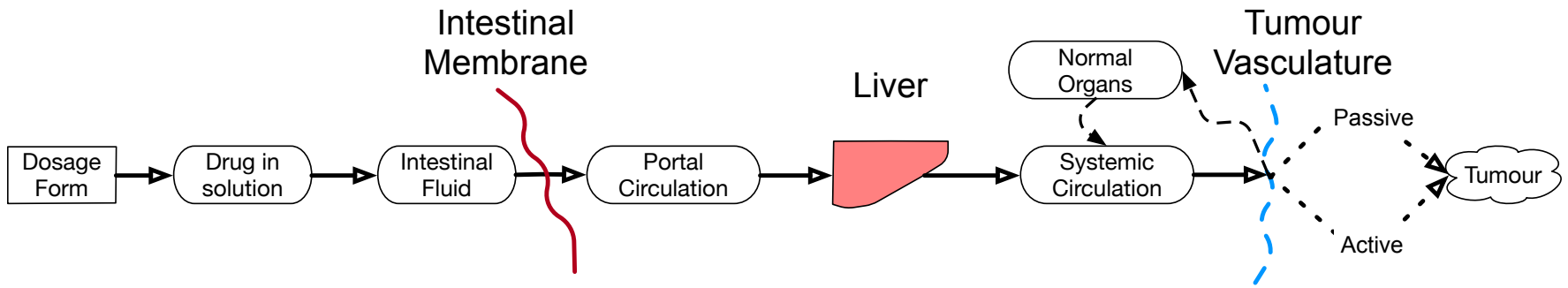
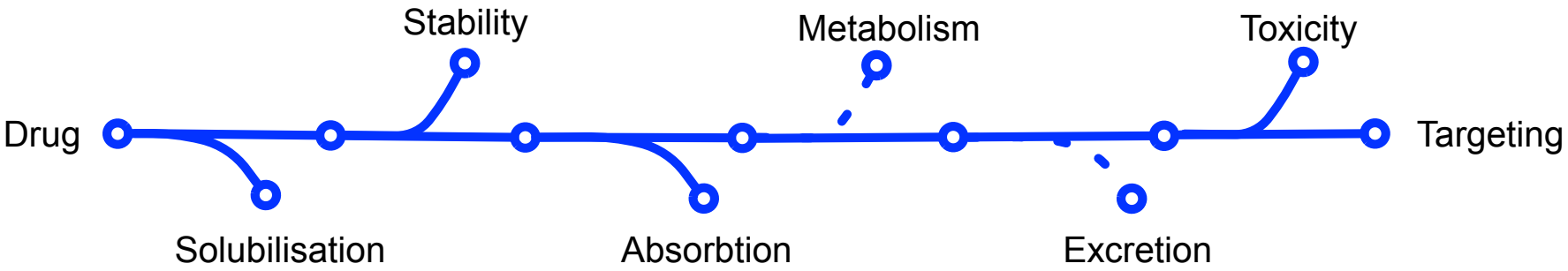
Barriers requiring carriers

How far do you need to go?





Use an excipient (carrier) to usurp or circumvent the barrier

Barriers requiring carriers

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Pharmaceutical nano-landscape

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Pharmaceutical nano-landscape

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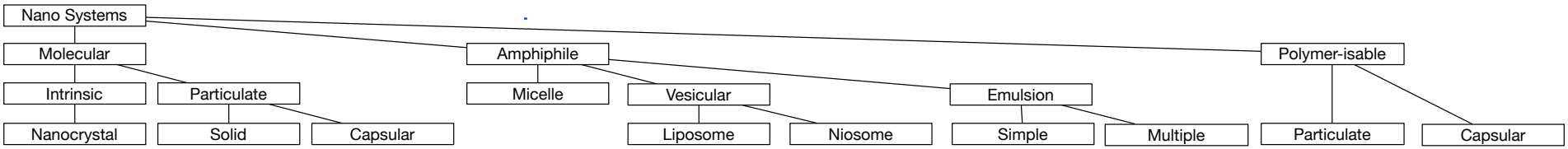
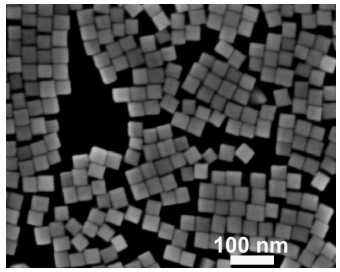
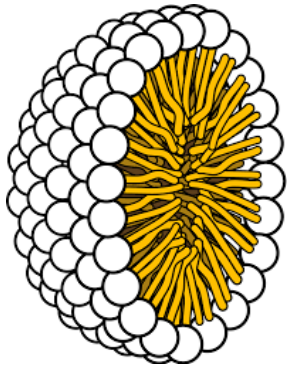


Nanocrystals



Micelles



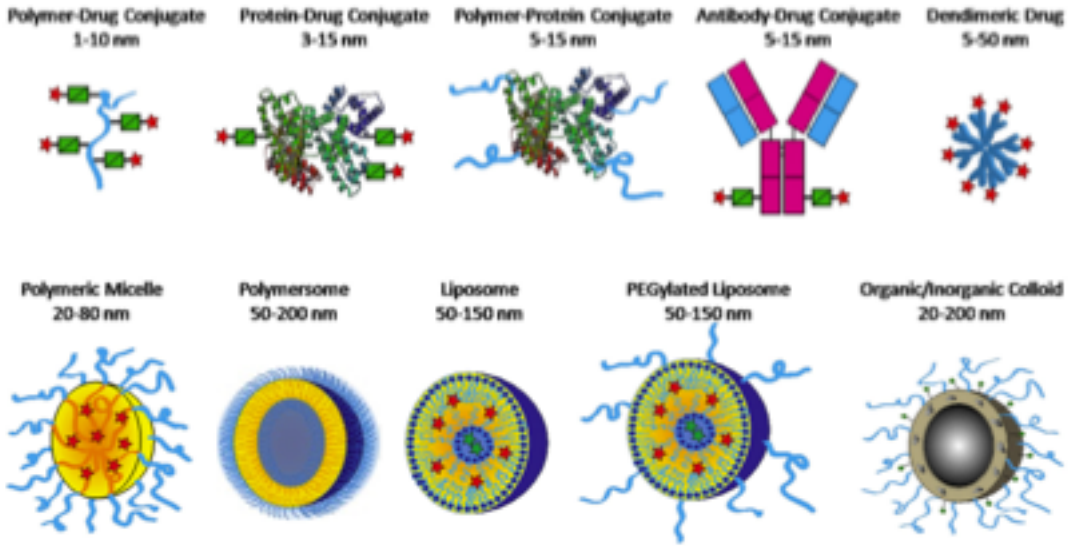


Figure 1 Schematic depiction of routinely used nanomedicine formulations. Note that most standard (chemotherapeutic) drug molecules are between 0.1 and 1 nm in hydrodynamic diameter.

Talelli, M., et.al., Nano Today 2015;10;93-117

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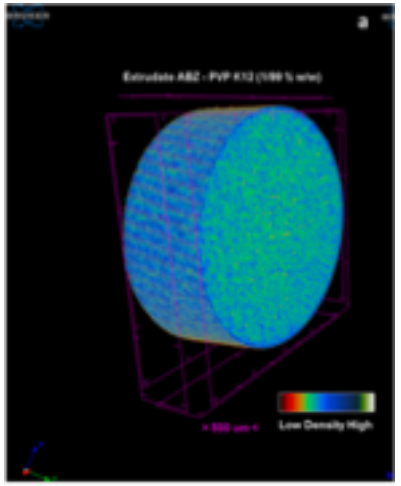
Pharmaceutical nano-landscape

Amorphous systems

- Are they nanobased?
  - Drug dispersed in polymer – nano sized domains
  - Molecular dispersion or solution
- Route to increased kinetic solubility
- Systems variability possible
  - Nano-crystalline to amorphous
  - Polymer characteristics
- Extreme particle size reduction
  - Down to the molecule
  - NB also applicable for other systems



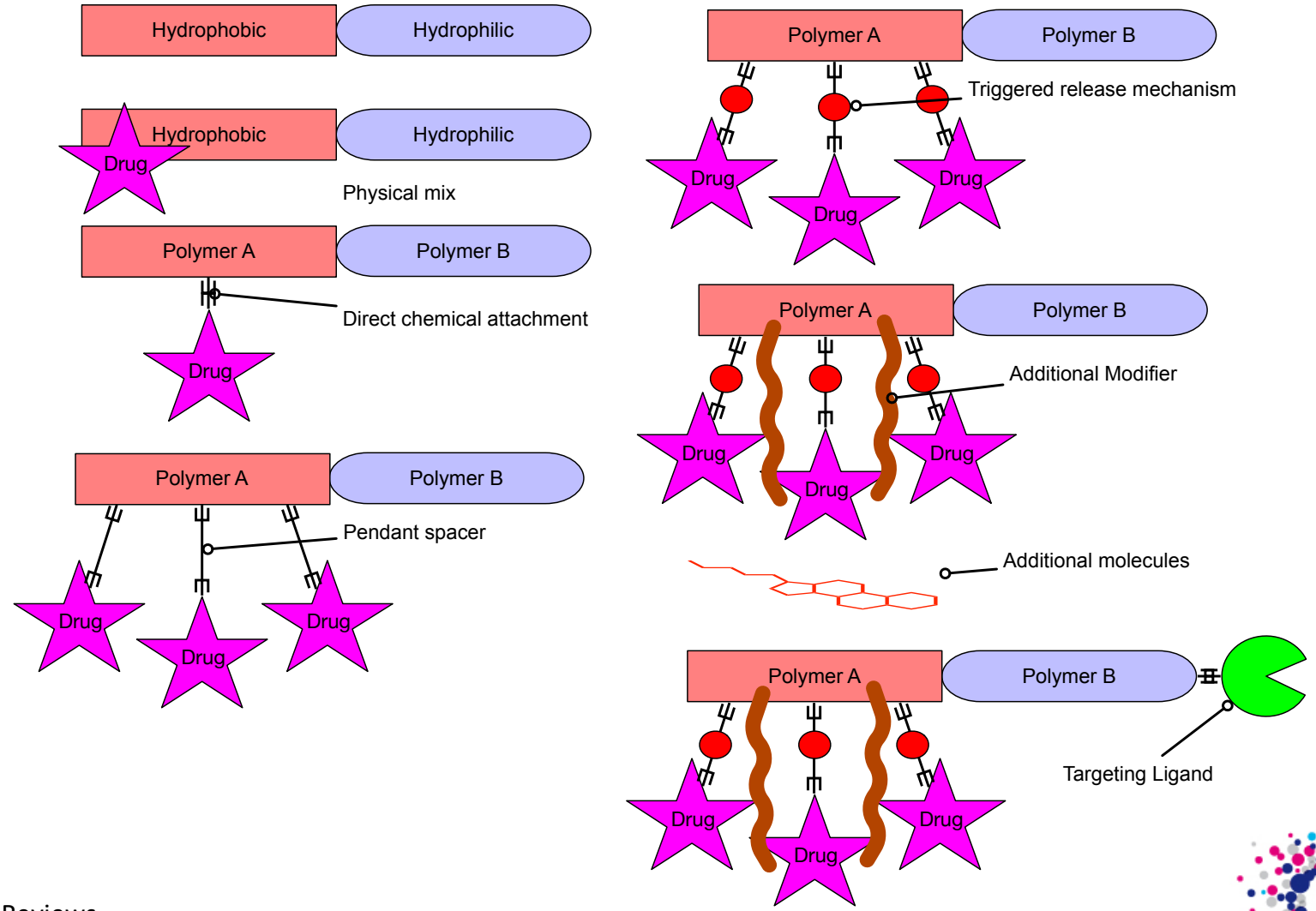
Albendazole polymer – amorphous dispersion

Martinez-Marcos, L., et.al., Int.J.Pharm., 2016;499;175-185

Review
Jermain, S.V., et.al., Int.J.Pharm., 2018;535;379-392

Pharmaceutical nano-landscape

Development of polymeric systems



Reviews
Perez-Herrero, E., et.al., Eur.J.PharmSci., 2015;93;52-79
Biswas, S et.al., Eur.J.PharmSci., 2016;83;184-202

Pharmaceutical nanolandscape

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Amorphous, anthracyclines and taxanes

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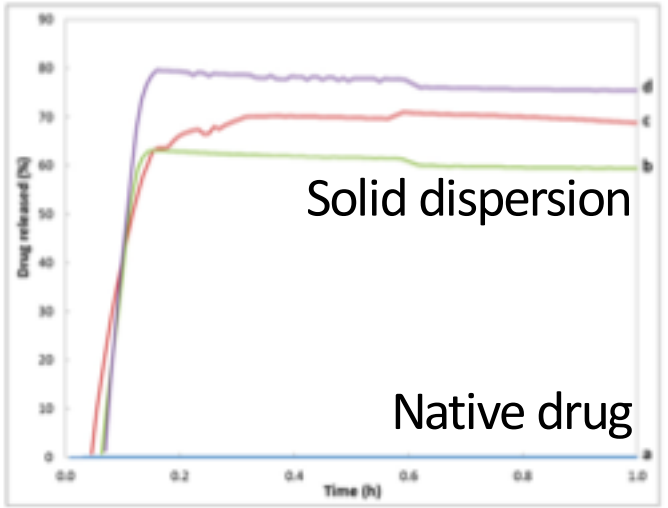
Amorphous systems

- Increased interest
  - Poorly soluble drugs
- Range of manufacturing techniques
  - Hot melt extrusion, solvent precipitation
- Example marketed systems
  - Vemurafenib
  - Regorafenib
  - Evorlimus
- Solubility assistance only

Dissolution of Albendazole



Martinez-Marcos, L., et.al., Int.J.Pharm., 2016;499;175-185

Amorphous, anthracyclines and taxanes

PAMAM-Doxorubicin dendrimer

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- Oral administration 20mg/kg in rat
- Particle size ≈ 4nm
- Doxorubicin

  Cmax (µM) = 0.20

  AUC (µg/mL)*h = 0.78
- Doxorubicin-PAMAM

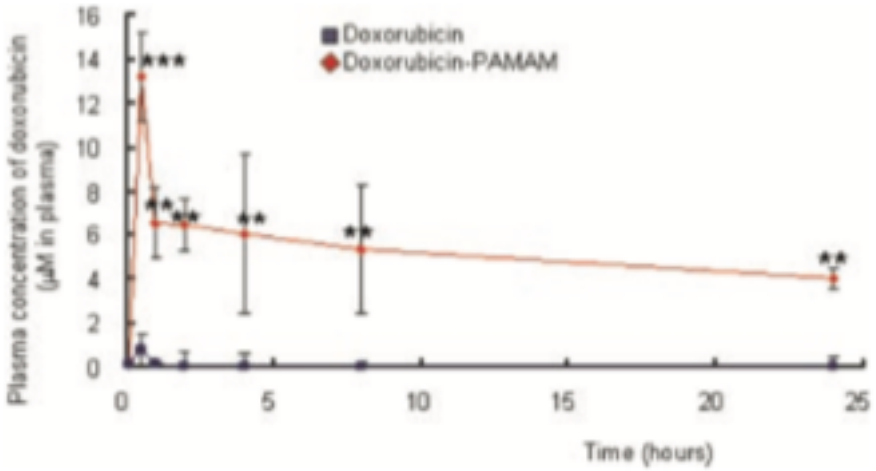
  Cmax (µM) = 7.63

  AUC (µg/mL)*h = 247
- Doxorubicin IV

  Cmax (µM) ≈ 10

Data from: Rahman, A., et.al., Cancer.Res., 1986;46;2295-2299

Data from: Ke, W., et.al., J.Pharm.Sci., 2008;97;2208-2216



Relative not Absolute!

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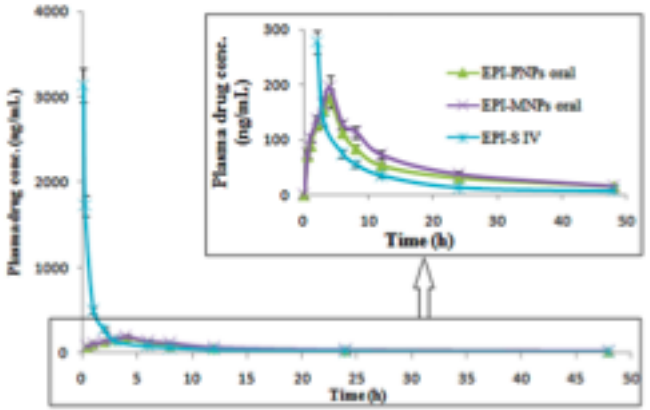
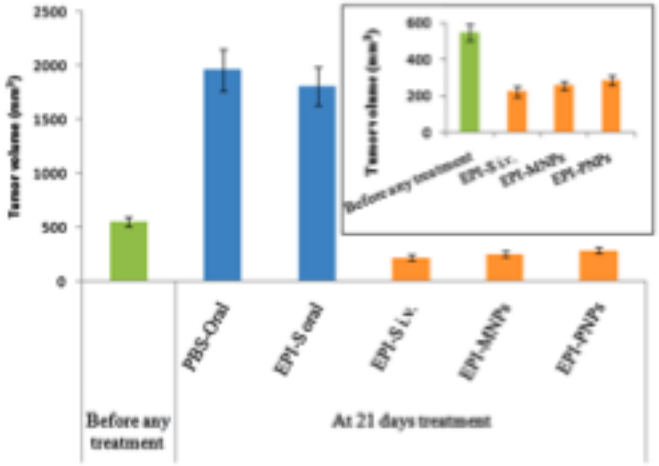
Amorphous, anthracyclines and taxanes

Surface decorated nanoparticles

- PLGA Nanoparticles
- Surface –polyethylene glycol or mannosamine
- Epirubicin @ 10mg/kg in rats
- Particle Size ≈ 250nm





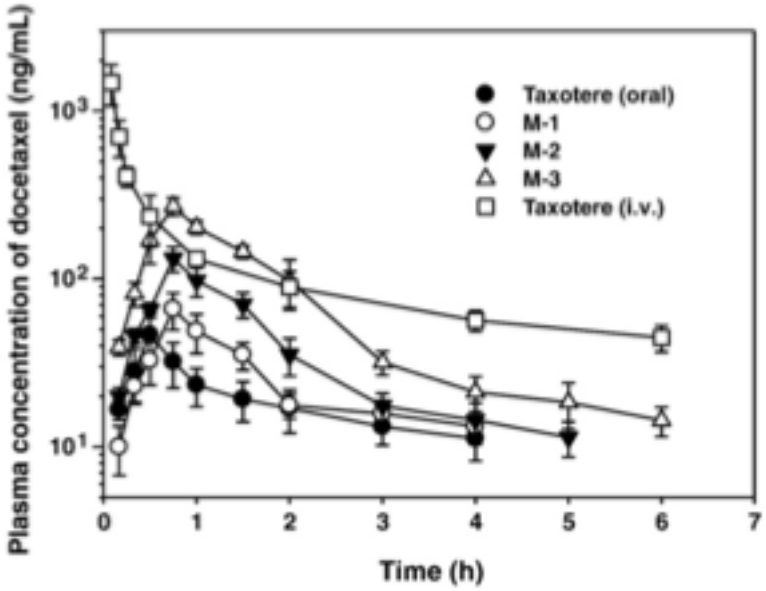
Parameters	EPI-S IV	EPI-S oral*	EPI-PNPs oral	EPI-MNPs oral
C_{max} (ng/mL)	3133.3 ± 256.23	132.52 ± 12.66*	174.62 ± 18.32	194.87 ± 21.32
T_{max} (h)	1.16 ± 0.4	3.833 ± 0.4 h*	4.33 ± 0.86	4.33 ± 0.86
AUC_{0-t} (ng h/mL)	2956.08 ± 300.64	512.16 ± 56.32*	2258.57 ± 154.08	2722.93 ± 192.85
$AUC_{0-\infty}$ (ng h/mL)	3094.24 ± 312.45	551.5 ± 64.05*	2592.1 ± 180.3	3072.74 ± 340.21

Data from: Tariq, M., et.al., Int.J.Pharm., 2016;501;18-31

Amorphous, anthracyclines and taxanes

Docetaxel microemulsion

- o/w microemulsion oral in rats
  Capryol 90/cremophor/transcutol
- Droplet size ≈ 30nm



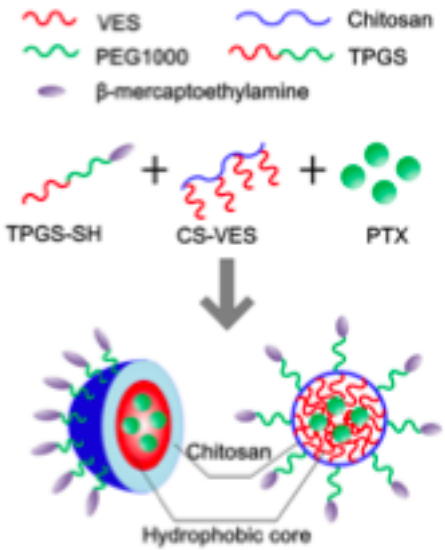
po 10 mg/kg

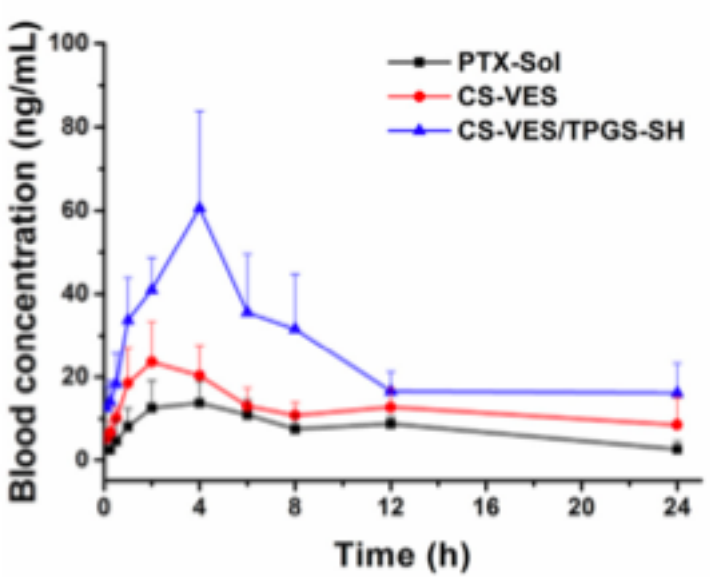
iv 8mg/kg

Yin, Y-M., et.al., J.Cont.Rel., 2009;140;86-94

Paclitaxel nanomicelle

- Dual functional system – in rats
  Mucosal penetration & P-gp inhibition
- Particle size ≈ 250nm





po 15 mg/kg

Lian, H., et.al., Colloids and Surfaces B: Biointerfaces, 2017;155;429-439

Amorphous, anthracyclines and taxanes

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Nanotechnology issues

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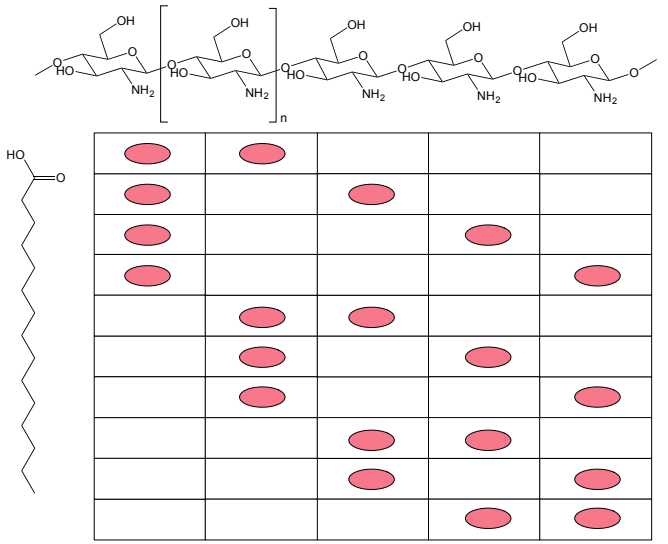
Nanotechnology issues

- Complex systems
- Production
  Solvent, dialysis, sonication, centrifugation
- Issues of scale up
  Working volume approx 10mL
- Control of complex polymers
  Synthesis and impact on properties
- Stability
  Chemical and physical
- Cost of goods
  Greater than drug costs?
- Toxicity



Realistic values ≈ 10^n

Conclusions

- Not yet - “set the heather alight!”
  Struggling to break through
- Amorphous systems
  Increasing acceptance – solubility only – or maybe not?
- Experimental promise – not realized clinically
- Not simply drug – but whole system
  Efficacy, variability, biological interaction, manufacture and control
- Likely to arrive
  Bioavailability improvement
- Watch this space

Recent Quote
Despite the demonstrated advantages by the preclinical studies, further studies on improved understanding of the interactions of SLNCs with biological tissues of the target site is necessary for efficient designing functional nanoparticles for clinical applications. Mu, H., Holm, R., Expert Opinion Drug Delivery 2018;15;771-785

Reviews
Tran, S., et.al., Clin.Trans.Med., 2017;6;44
Ventola, C.L., P&T., 2017;42;742-755

Thank you

- Funder – Cancer Research UK
- Collaborators
  - Many and varied
    - Local, national and international
- Organisers - Invitation
- You for listening